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Myo-inositol lowers the risk of developing gestational diabetic mellitus in pregnancies: A systematic review and meta-analysis of randomized controlled trials with trial sequential analysis

Xianshan Guo [a], Shizhe Guo [b], Zhiyi Miao [c], Zhen Li [d,*], Hongya Zhang [e,*]

[a] Department of Endocrinology, Xinxiang Central Hospital, Xinxiang, Henan 453000, China
[b] Department of Endocrinology and Metabolism, Huashan Hospital, Fudan University, Shanghai 200040, China
[c] School of Economics, Fudan University, Shanghai 200433, China
[d] Department of General Surgery, Yangpu Hospital, Tongji University School of Medicine, Shanghai 200090, China
[e] Central Laboratory, Yang Pu District Center of Disease Control and Prevention, Shanghai 200090, China

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ABSTRACT

Aims: to explore the potential benefit of myo-inositol on pregnant women with high risk of developing gestational diabetes mellitus (GDM).
Methods: Pubmed, Embase, and Cochrane library were systematically searched for randomized controlled trials (RCTs) comparing myo-inositol with placebo for pregnant women with risk factors of GDM. Primary outcome were the incidence of GDM and birth weight. Secondary outcomes included fasting, 1 h, and 2 h oral glucose tolerance test (OGTT), and complications. Trial sequential analysis (TSA) was performed on primary outcomes to confirm the pooled results. Number needed to treat (NNT) was calculated to show the efficacy of myo-inositol supplement.
Results: Four RCTs with 586 patients were included. Compared with placebo, patients with myo-inositol supplement had significantly lower the risk of developing GDM (RR = 0.44, 95% CI [0.32, 0.62], $P < 0.0001$) without heterogeneity ($I^2 = 0\%$, $P = 0.99$), which was confirmed by TSA. NNT was 6.2 and rounded to 7. Myo-inositol did not significantly decrease birth weight (60.60 g, 95% CI [−177.21, 56.02], $P = 0.31$) with significant heterogeneity ($I^2 = 52\%$, $P = 0.12$), but was not confirmed by TSA. Myo-inositol supplement was related to significantly lower fasting, 1 h, and 2 h OGTT value and the incidence of pre-term delivery. Difference was not significant between myo-inositol and placebo regarding incidence of other complications.
Conclusion: Myo-inositol is related to lower incidence of GDM, as well as fasting, 1 h, and 2 h OGTT value, in pregnant women with high risk of this condition. Myo-inositol might not be related to a lower birth weight, which needs further confirmation.

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* Corresponding authors at: Department of General Surgery, Yangpu Hospital, Tongji University School of Medicine, Shanghai 200090, China.
E-mail addresses: lizhen3829@126.com (Z. Li), zhy3829@163.com (H. Zhang).

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1. Introduction

Gestational diabetes mellitus (GDM), one of the most common pregnancy complications, is defined as glucose intolerance with onset or first recognition during pregnancy.[27] The prevalence of GDM is rising together with the increasing prevalence of type 2 diabetes and obesity around the world.[14] Current evidence indicates that GDM is associated with high risk for both fetus and gravida, including macrosomia, neonatal hypoglycemia, hyperbilirubinemia for baby and a tendency to obesity, diabetes mellitus and metabolic syndrome for mom.[29] Evidences unveil that GDM is strongly associated with advancing age, elevated body mass index (being overweight or obesity), and history of first-degree type 2 diabetes.[13] Besides, pregnant women with polycystic ovary syndrome (PCOS) are at higher risk for development of GDM.[35] In spite of so many adverse outcomes and accelerating incidence, the mechanism for GDM remains unrevealed. Effective prevention modalities for high-risk population are required. (See Table 1.)

Myo-inositol is an isomer of inositol which naturally occurs in kinds of foods such as cereals, corn, beans and meat. It enhances insulin action since it acts as the precursor of inositolphosphoglycans (IPG), a second messenger for insulin.[4] IPG is vital for activation of enzymes that is related to glucose uptake and usage.[1] Previous research has identified the salutary effects of myo-inositol supplementation in improving several of the hormonal and reproductive disturbances of PCOS.[36] However, the benefit of myo-inositol for pregnant women with high risk of GDM is still poorly studied.

Several randomized controlled trials (RCTs) have focused on the target population with, however, different observations. Facchineti et al. failed to show that myo-inositol can reduce the incidence of GDM,[12] but was opposed by others. D Anna et al. observed a significant decline of birth weight in pregnant women compared with placebo,[11] and was inconsistent with similar researches. Therefore, a systematic review and meta-analysis is performed to summarize and figure out the potential gain of supplementary myo-inositol.

2. Materials and methods

This systematic review was organized in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist.[23]

2.1. Search strategy

The first two authors independently searched on February 6th, 2017 on Pubmed, Embase, and Cochrane library. The key words were gestational, diabetic mellitus, diabetes, myo-inositol, and myoinositol. Reference lists of relevant systematic reviews were also scanned.

Table 1
Basic characteristics of included studies.

Study	Inclusion criteria	Number of patients		Age		Intervention protocol	
		Experimental	Control	Experimental	Control	Experimental	Control
D ANNA 2015	1) pre-pregnancy body mass index (BMI) (calculated as weight (kg)/[height (m)]^2) 30 or greater 2) singleton gestation	110	110	30.9 (18–44)[a]	31.7 (19–43)[a]	2 g myo-inositol plus 200 mg folic acid twice a day until delivery	200 mg folic acid twice a day until delivery
SANTAMARIA 2015	1) pre-pregnancy BMI > 25 and <30 kg/m^2 2) first trimester fasting plasma glucose ≤126 mg/dl and/or random glycemia <200 mg/dl 3) single pregnancy and 4) Caucasian ethnicity	110	110	32.1 ± 4.8[b]	32.7 ± 5.3[b]	2 g myo-inositol plus 200 mg folic acid twice a day from the first trimester to delivery	200 mg folic acid twice a day from the first trimester to delivery
FACCHINETTI 2013	1) Single pregnant women with BMI > 27 2) normal glucose and Glycosylated Hemoglobin	31	60	NA	NA	2 g myo-inositol plus 200 mg folic acid twice a day from first prenatal exam to11th week of pregnancy	200 mg folic acid twice a day from first prenatal exam to11th week of pregnancy
D ANNA 2013	1) first-degree relatives affected by type 2 diabetes 2) pre-pregnancy BMI < 30 kg/m^2 3) fasting plasma glucose <126 mg/dl and random glycemia <200 mg/dl 4) single Caucasian pregnancy	110	110	31 ± 5.3[b]	31.6 ± 5.6[b]	2 g myo-inositol plus 200 mg folic acid twice a day from the end of the first trimester	200 mg folic acid twice a day from the end of the first trimester

NA: not available.
[a] Data are median (range).
[b] Data are mean ± standard deviation.

2.2. Trial inclusion and data extraction

RCTs comparing myo-inositol with placebo for pregnant women without DM or a history of DM were included. Except for folic acid that is unavoidably administered to pregnancies,[26] RCTs in which patients took other any supplements were excluded. The first two authors reviewed all titles and abstracts in a cross-check manner. In case of insufficient information to make a decision, full-text would be retrieved. The same authors independently extracted data from included RCTs including name of first author, number of patients included, age, body mass index (BMI), percentage of nulliparous, detailed intervention protocols, outcome measures, and included population. Primary outcome were the incidence of GDM, and birth weight. Secondary outcomes were fasting oral glucose tolerance test (OGTT), 1 h glucose OGTT, and 2 h glucose OGTT, and complications that were reported in a former review.[38]

2.3. Data analysis

A random-effects model was used for all comparisons because population, detailed intervention methods, and other factors were inconsistent across RCTs. Difference in binary outcomes were calculate by relative risk (RR) and 95% confidence interval (CI), while that in continuous variables were compared by mean difference (MD) and 95% CI. Heterogeneity was assessed by Q statistic and I^2 statistic. Comparisons with an I^2 statistic larger than 50% were considered to have significant heterogeneity.[21] When significant heterogeneity was observed in the pooled primary outcome, sensitivity analysis was performed by omitting each trial in each turn to figure out the potential source of heterogeneity. Because of the limited number of RCTs included, publication bias was not detected.[31] A two-tail p value <0.05 indicates statistical significance. Analyses were performed using Review Manager, Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration; Copenhagen, Denmark). Once a significant difference between myo-inositol supplement and placebo was observed, a post hoc calculation of number need to treat (NNT) was conducted to show the relative treatment effectiveness of myo-inositol for preventing GDM.

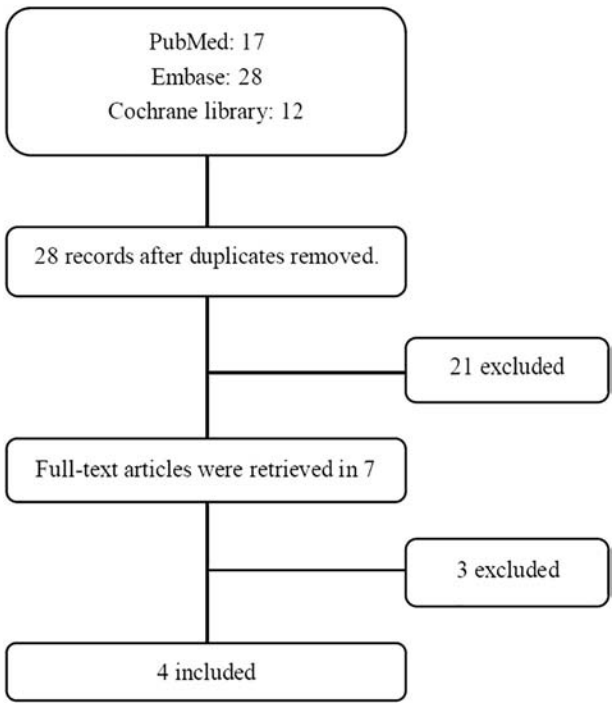

Fig. 1. Flow chart of study selection.

2.4. Quality assessment

The first two reviewers independently used the Cochrane's risk of bias tool to evaluate the quality of each included study.[20] Agreement was achieved by discussion. The degree of agreement was expressed as the κ value. A κ between 0.40 and 0.59 was fair, 0.60 and 0.74 as good, 0.75 and 1 as excellent.[20] A value of low, unclear or high risk of bias was assigned to the seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

The quality of evidence of the primary outcome was evaluated by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. The level of evidence was entitled as high, moderate, low, or very low, according to five sections including risk of bias, imprecision, indirectness, heterogeneity, and publication bias.[15–19] Publication bias could not be assessed, and evidence was downgraded when heterogeneity was >40%.[17]

2.5. Trial sequential analysis

The type one error was increased by sparse data and repeated significance testing, which was a shortcoming of traditional meta-analyses.[2,3,33,34] On ground of this, trial sequential analysis (TSA), which was based on the sample size of meta-analysis, was conducted in the current meta-analysis to strengthen the pooled result of primary outcome. The diversity-adjusted required information size (DIS) with the eventual breach of the cumulative Z-curve of the relevant trial sequential monitoring boundaries was calculated to provide a required information size (RIS) as well as a threshold for a treating effect with statistical significance.[37]

The RIS of the incidence of GDM was calculated based on a relative risk reduction of 20%, and that of birth weight was estimated based on the empirical method. The control event rates were calculated from the placebo group. The analysis was conducted with the use of TSA version 0.9 beta software (TSA software version 0.9 Beta; Copenhagen Trial Unit, Copenhagen, Denmark). The type I error (α) was set as 0.05 with a power of 0.80.[37]

3. Results

The initial search yielded 28 titles. Full text of 7 studies was retrieved after reading titles and abstracts, of which four RCTs were included finally.[9,11,12,30] (Fig. 1) One was excluded because of additional supplements intake,[24] one because of patients already with diabetic mellitus,[25] and one with a non-randomized study design.[10] A total of 586 patients were included. The summary of risk of bias is shown in Fig. 2. The kappa value was 0.9, indicating an excellent agreement between two reviewers. The risk of bias of included studies was shown in Fig. 2. All studies described the randomization method, except for one RCT which was an interim report in abstract, hence introducing high or unclear bias into all domains.[12] No study kept blinding of participants, personnel, and doctors who were responsible for outcome measurements.

The pooled evidence suggested that, compared with placebo, myo-inositol supplement is associated with a reduced the risk of developing GDM (RR = 0.44, 95% CI [0.32, 0.62], $P < 0.0001$) without significant heterogeneity ($I^2 = 0\%$, $P = 0.99$) (Fig. 3), which was confirmed by TSA results (Fig. 4). The level of evidence was moderate, as a consequence of random effect model, which implied a potential imprecision. Subgroup analysis showed that, the number need to treat (NNT) was 6.2 and was rounded to the next higher whole

Fig. 2. Risk bias of included studies.

number 7. This implied that after every seven cases of pregnant women with high risk of GDM receiving supplementary myo-inositol, one additional treatment success was acquired, as compared with placebo treatment.

Besides, the pooled results found that myo-inositol was not related to a significant decrease the birth weight (MD = −60.60 g, 95% CI [−177.21, 56.02], $P = 0.31$) with significant heterogeneity ($I^2 = 52\%$, $P = 0.12$) (Fig. 5), but this finding was not confirmed by TSA (Fig. 6). The level of evidence was low, as a consequence of heterogeneity as well as imprecision.

In the RCTs reporting OGTT value, the time point of conducting OGTT was approximately 26 weeks of gestational age, indicating a consistency among included RCTs. The pooled outcomes revealed that myo-inositol was related to significantly lower fasting OGTT (MD = −0.18, 95% CI [−0.24, −0.12], $P < 0.00001$) without significant heterogeneity ($I^2 = 0\%$, $P = 0.59$) (Appendix 1, Figure 1), 1 h OGTT (MD = −0.55, 95% CI [−0.81, −0.28], $P < 0.00001$) without significant heterogeneity ($I^2 = 0\%$, $P = 0.50$) (Appendix 1, Figure 2), and 2 h OGTT (MD = −0.58, 95% CI [−0.94, −0.23], $P = 0.001$) with significant heterogeneity ($I^2 = 60\%$, $P = 0.06$) (Appendix 1, Figure 3). Supplementary myo-inositol was associated with significantly lower incidence of pre-term delivery (RR = 0.30, 95% CI [0.11, 0.79], $P = 0.01$) without significant heterogeneity ($I^2 = 0\%$, $P = 0.86$). However, patients who took myo-inositol supplement did not show a significantly decreased incidence in other complications, including distress respiratory syndrome, macrosomia, shoulder dystocia, and neonatal hypoglycemia (Appendix 1, Figure 4).

4. Discussion

The present meta-analysis shows that, for non-diabetic pregnant women with high risk of developing GDM, patients who received supplementary myo-inositol had lower incidence of GDM compared with those received placebo. This beneficial effect is robust, as indicated by TSA. The birth weight is not significantly influenced by myo-inositol supplement. However, the level of evidence was low and TSA suggests that this finding needs further researches. Besides, the supplement is associated with a lower value of fasting, 1 h, and 2 h OGTT. It's relationship with complication rate needs more reports.

Previously, two systematic reviews and meta-analyses have focused on the same topic. Although both reviews drew a same conclusion regarding the incidence of GDM, the inclusion criterias of clinical trials were not identical. Zheng et al. enrolled controlled trials in which one recruited patients that already had GDM.[38] Besides, the incidence of abnormal OGTT was input as the incidence of GDM, undermining the pooled result. Crawford et al. only analyzed RCTs.[7] However, trials compared the administration of any dose of myo-inositol either alone or in combination preparation were included, introducing inconsistency into conclusion. In the current review, only RCTs in which myo-inositol alone compared to placebo were eligible. What's more, three comprehensive databases were searched, minimizing potential searching bias to the lowest extent.

Myo-inositol has been proven to be effective to improve metabolic disorders.[8] Similar to previous findings, we found that, for pregnant women with high risk of developing abnormal metabolic profiles, the incidence of GDM declined after an additional intake of myo-inostiol. To further illuminate the effect of this supplement, we calculated NNT. An NNT value of 7, which was <10, suggests that this is a beneficial option in this condition.[6] Patients in myo-inositol group had

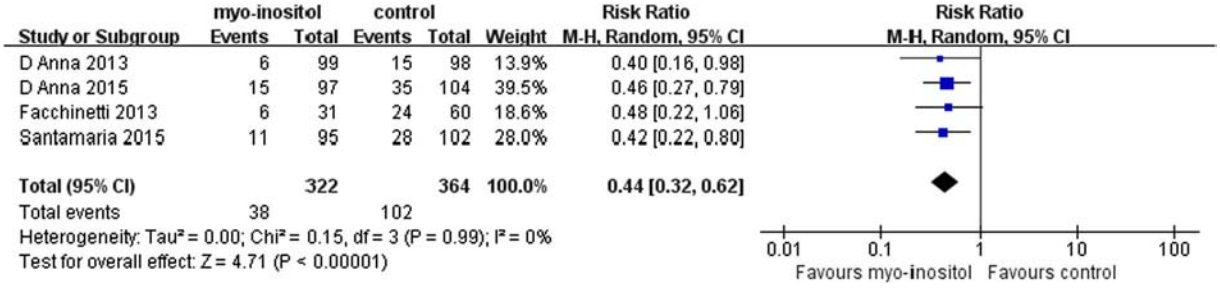

Fig. 3. Meta-analysis of the difference in the incidence of gestational diabetes mellitus.

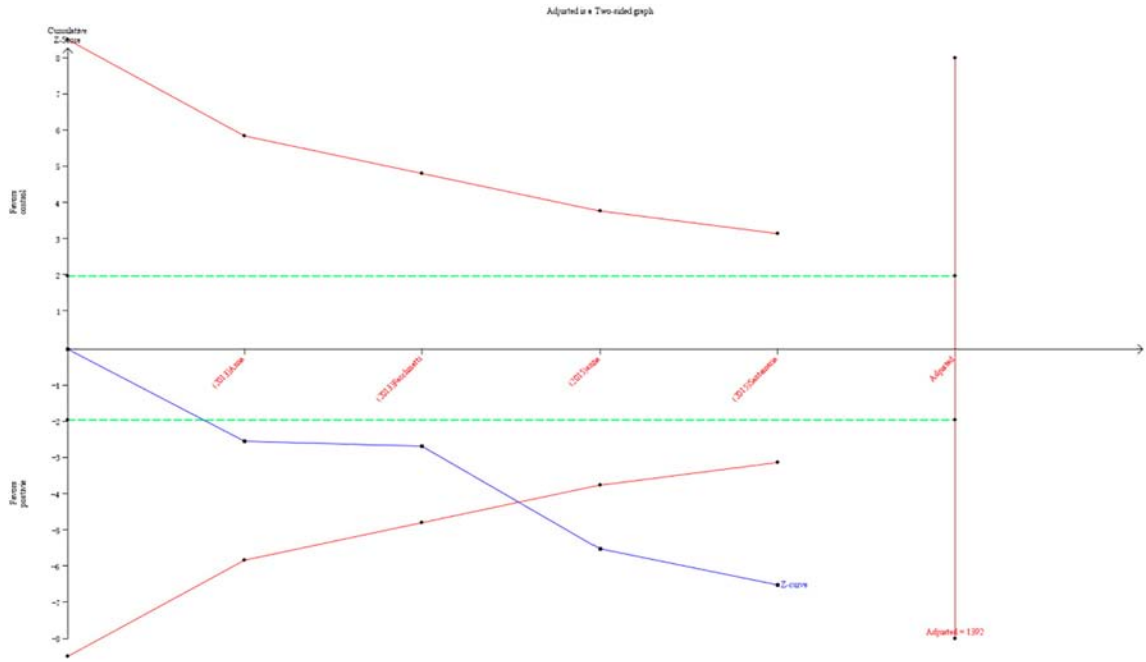

Fig. 4. Trial sequential analysis of the pooled outcome regarding the pooled outcome of the difference in the incidence of gestational diabetes mellitus. TSA showed that the pooled results (z-curve, blue curve) crossed the conventional boundary of benefit (green dotted line), the trial sequential monitoring boundary for benefit (red curve), and the required sample size based on TSA, entering the area of benefit (below the lower red line).

lower OGTT at three time points than those in placebo group, which might be attributed to the insulin sensitizing effect of myo-inositol.

No single complication, other than pre-term delivery, reaches significance in this meta-analysis. We think this outcome may be a consequence of limited sample size and, subsequently, the small number of complication reports. However, it is impossible to pool all complications together for the purpose of enlarging sample size, as one may had more than one complication at the same time. On ground of incidence of complications, it might be difficult to delineate the effect of myo-inositol supplement.

Another modality to avoid the influence of sample size, as well as the repeated measures, is the TSA. TSA is an increasingly popular method to strengthen the result of meta-analysis.[2,32] We found that for the incidence of GDM, although the sample size as a whole did not reach the TSA required information size, the significance has already been confirmed, indicating reliability. On the contrary, meta-analysis suggests that myo-inositol reduced birth weight insignificantly, which was questioned by TSA. Therefore the impact of myo-inositol on neonates needs more follow-up.

Apart from the measurements to reinforce the results, the systematic review and meta-analysis has several limitations. First, all RCTs included were reported by European groups, and Caucasian women take the highest proportion. Given that the effect of myo-inositol on one disorder may vary depending on population,[1,5] whether this supplement can be administrated to other ethnicities remains poorly understood. Besides, albeit the fact that the patients analyzed had high risk of developing metabolic disorders and GDM, the mechanism underlying the condition differs.[22,28] Therefore, albeit a robust relationship between myo-inositol supplement with decreased GDM incidence ascertained by TSA, well-designed clinical trials are required to illustrate the pros and cons of this administration based on individual profiles.

5. Conclusion

Myo-inositol is related to lower incidence of GDM, as well as fasting, 1 h, and 2 h OGTT value, in pregnant women with high risk of this condition. Myo-inositol might not be related to a lower birth weight, which needs further confirmation.

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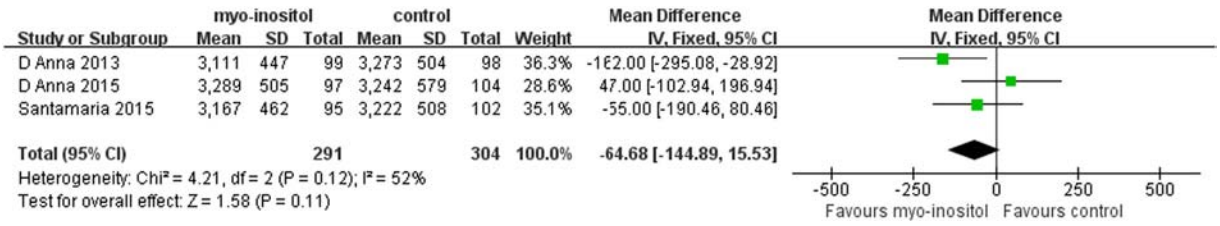

Fig. 5. Meta-analysis of the difference in birth weight.

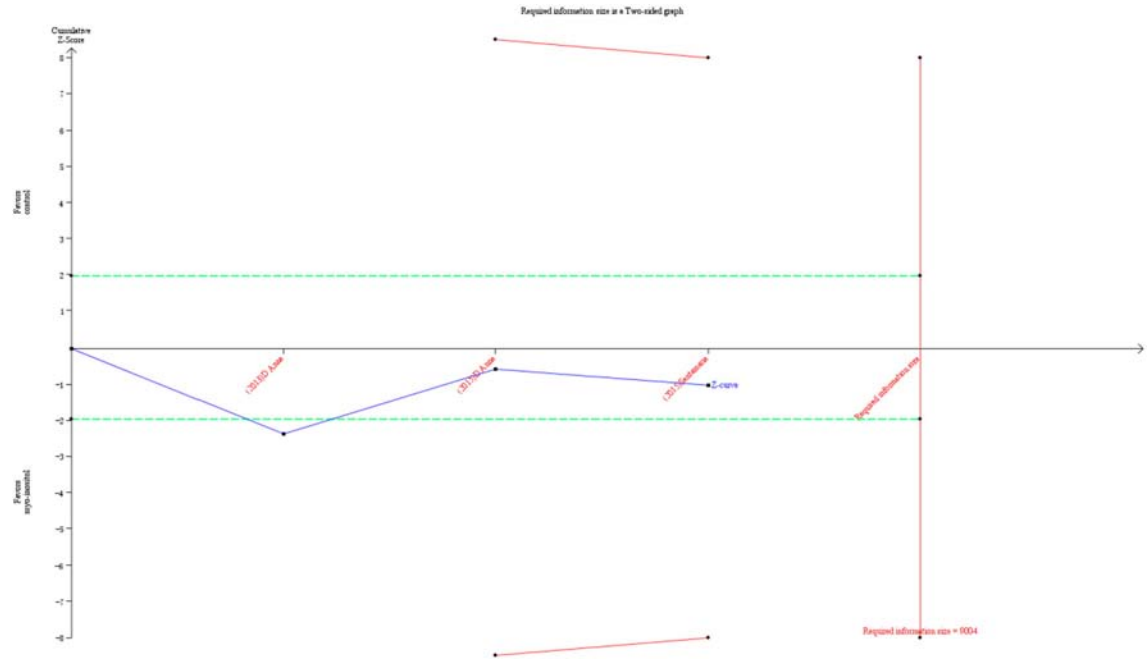

Fig. 6. Trial sequential analysis of the pooled outcome regarding the pooled outcome of the difference in birth weight. TSA showed that the pooled results (z-curve, blue curve) did not cross the conventional boundary of benefit (green dotted line), the trial sequential monitoring boundary for benefit (red curve), or the required sample size based on TSA, and failed to enter the area of benefit (below the lower red line).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jdiacomp.2017.07.007.

References

1. Baillargeon JP, Iuorno MJ, Apridonidze T, Nestler JE. Uncoupling between insulin and release of a D-chiro-inositol-containing inositolphosphoglycan mediator of insulin action in obese women with polycystic ovary syndrome. *Metab Syndr Relat Disord.* 2010;8:127-36.
2. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol.* 2008;61:763-9.
3. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive–trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol.* 2009;38:287-98.
4. Buttner J. Johann Joseph von Scherer (1814-69). The early history of clinical chemistry. *J Clin Chem Clin Biochem.* 1978;16:478-83.
5. Cheang KI, Baillargeon JP, Essah PA, Jr Ostlund ER, Apridonize T, Islam L, et al. Insulin-stimulated release of D-chiro-inositol-containing inositolphosphoglycan mediator correlates with insulin sensitivity in women with polycystic ovary syndrome. *Metabolism.* 2008;57:1390-7.
6. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Int J Clin Pract.* 2013;67:407-11.
7. Crawford TJ, Crowther CA, Alsweiler J, Brown J. Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes. *Cochrane Database Syst Rev.* 2015:Cd011507.
8. Croze ML, Soulage CO. Potential role and therapeutic interests of myo-inositol in metabolic diseases. *Biochimie.* 2013;95:1811-27.
9. D'Anna R, Benedetto A, Scilipoti A, Santamaria A, Interdonato ML, Petrella E, et al. Myo-inositol supplementation for prevention of gestational diabetes in obese pregnant women: A randomized controlled trial. *Obstet Gynecol.* 2015;126:310-5.
10. D'Anna R, Di Benedetto V, Rizzo P, Raffone E, Interdonato ML, Corrado E, et al. Myo-inositol may prevent gestational diabetes in PCOS women. *Gynecol Endocrinol.* 2012;28:440-2.
11. D'Anna R, Scilipoti A, Giordano D, Caruso C, Cannata ML, Interdonato ML, et al. Myo-inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes: A prospective, randomized, placebo-controlled study. *Diabetes Care.* 2013;36:854-7.
12. Facchinetti F, Pignatti L, Interdonato M, Neri I, Bellei G, D'Anna R. Myoinositol supplementation in pregnancies at risk for gestational diabetes. Interim analysis of a randomized controlled trial (RCT). *Am J Obstet Gynecol.* 2013;208:S36.
13. Fatima SS, Rehman R, Alam F, Madhani S, Chaudhry B, Khan TA. Gestational diabetes mellitus and the predisposing factors. *J Pak Med Assoc.* 2017;67:261-5.
14. Ferrara A. Increasing prevalence of gestational diabetes mellitus: A public health perspective. *Diabetes Care.* 2007;30:S141-146.
15. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence–imprecision. *J Clin Epidemiol.* 2011;64:1283-93.
16. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence–indirectness. *J Clin Epidemiol.* 2011;64:1303-10.
17. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence–inconsistency. *J Clin Epidemiol.* 2011;64:1294-302.
18. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence–publication bias. *J Clin Epidemiol.* 2011;64:1277-82.
19. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence–study limitations (risk of bias). *J Clin Epidemiol.* 2011;64:407-15.
20. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557-60.
22. Krishnan A, Muthusami S. Hormonal alterations in PCOS and its influence on bone metabolism. *J Endocrinol.* 2017;232:R99-113.
23. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Loannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ.* 2009;339:b2700.
24. Malvasi A, Casciaro F, Minervini MM, Kosmas I, Mynbaev OA, Mynbaev OA, et al. Myo-inositol, D-chiro-inositol, folic acid and manganese in second trimester of pregnancy: A preliminary investigation. *Eur Rev Med Pharmacol Sci.* 2014;18:270-4.
25. Matarrelli B, Vitacolonna E, D'Angelo M, Pavone G, Mattei PA, Liberati M, et al. Effect of dietary myo-inositol supplementation in pregnancy on the incidence of maternal gestational diabetes mellitus and fetal outcomes: A randomized controlled trial. *J Matern Fetal Neonatal Med.* 2013;26:967-72.
26. McStay CL, Prescott SL, Bower C, Palmer DJ. Maternal folic acid supplementation during pregnancy and childhood allergic disease outcomes: A question of timing? *Forum Nutr.* 2017;9.
27. Metzger BE, Coustan DR. Summary and recommendations of the fourth international workshop-conference on gestational diabetes mellitus. The organizing committee. *Diabetes Care.* 1998:B161-.
28. Ray I, Mahata SK, De RK. Obesity: An immunometabolic perspective. *Front Endocrinol (Lausanne).* 2016;7:157.
29. Reece EA, Leguizamon G, Wiznitzer A. Gestational diabetes: The need for a common ground. *Lancet.* 2009;373:1789-97.

30. Santamaria A, Benedetto A, Petrella E, Pintaudi B, Corrado F, D'Anna R, et al. Myo-inositol may prevent gestational diabetes onset in overweight women: A randomized, controlled trial. *J Matern Fetal Neonatal Med.* 2016;29:3234-7.
31. Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. *Health Technol Assess.* 2000;4:1-115.
32. Sun Y, Zhang P, Liu S, Li H, Jiang J, Chen S, et al. Intra-articular steroid injection for frozen shoulder. *Am J Sports Med.* 2017;45:2171-9.
33. Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Loannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? *Int J Epidemiol.* 2009;38:276-86.
34. Thorlund K, Imberger G, Walsh M, Chu R, Gluud C, Wetterslev J, et al. The number of patients and events required to limit the risk of overestimation of intervention effects in meta-analysis--a simulation study. *PLoS One.* 2011;6:e25491.
35. Toulis KA, Goulis DG, Kolibianakis EM, Venetis CA, Tarlatzis BC, Papadimas I. Risk of gestational diabetes mellitus in women with polycystic ovary syndrome: A systematic review and a meta-analysis. *Fertil Steril.* 2009;92:667-77.
36. Unfer V, Nestler JE, Kamenov ZA, Prapas N, Facchinetti F. Effects of inositol(s) in women with PCOS: A systematic review of randomized controlled trials. *Int J Endocrinol.* 2016;2016:1849162.
37. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol.* 2009;9:86.
38. Zheng X, Liu Z, Zhang Y, Lin Y, Song J, Zheng L, et al. Relationship between myo-inositol supplementary and gestational diabetes mellitus: A meta-analysis. *Medicine (Baltimore).* 2015;94:e1604.